Derivation of Inhibitory Nerve Cells from Human Embryonic Stem Cells

Grant Award Details

Derivation of Inhibitory Nerve Cells from Human Embryonic Stem Cells

Grant Type: Comprehensive Grant

Grant Number: RC1-00346

Investigator:

Name:	Arnold Kriegstein
Institution:	University of California, San Francisco
Type:	PI

Disease Focus: Parkinson's Disease, Neurological Disorders

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $2,410,874

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Grant Application Details

Application Title: Derivation of Inhibitory Nerve Cells from Human Embryonic Stem Cells

Public Abstract:

Parkinson's disease (PD) is caused by degeneration of a specific population of dopamine-producing nerve cells in the brain and is chronic, progressive, and incurable. Loss of dopamine-containing cells results in profound physiological disturbances producing tremors, rigidity, and severe deterioration of gate and balance. In the United States, approximately 1.5 million people suffer with PD and it is estimated that 60,000 new cases are diagnosed each year. Drugs can modify some of the disease symptoms, but many patients develop disabling drug-induced movements that are unresponsive to medication. Deep brain stimulation can alleviate motor symptoms in some patients but is not a cure. We plan an entirely novel approach to treat PD. We propose to utilize a specific class of inhibitory nerve cells found in the embryonic brain, known as MGE cells, as donor transplant cells to inhibit those brain regions whose activity is abnormally increased in PD. In preliminary studies we have demonstrated that this approach can relieve symptoms in an animal model of PD. To turn this approach into a patient therapy, we will need to develop methods to obtain large numbers of human cells suitable for transplantation. This proposal seeks to address this problem by producing unlimited numbers of exactly the right type of MGE nerve cell using human embryonic stem cells.

The inhibitory nerve cells we seek to produce will reduce brain activity in target regions. They may therefore be used to treat other conditions characterized by excessive brain activity, such as epilepsy. Epilepsy can be a life threatening and disabling condition. Nearly two million Americans suffer with some form of epilepsy. Unfortunately, modulation of brain excitability using antiepileptic drugs can have serious side-effects, especially in the developing brain, and many patients can only be improved by surgically removing areas of the brain containing the seizure focus. Using MGE cells made from human embryonic stem cell lines, we hope to develop a novel epilepsy treatment that could replace the need for surgery or possibly even drug therapy.

We propose an integrated approach that combines the complementary expertise of four UCSF laboratories to achieve our goals. We have already determined that mouse MGE cells can improve the symptoms of PD and epilepsy when grafted into animal models. We now need to develop methods to obtain large numbers of human cells suitable for grafting. We need to ensure that when delivered, the cells will migrate and integrate in the target brain regions, and we need to evaluate therapeutic efficacy in animal models of Parkinson's disease and epilepsy. This proposal addresses these goals. If successful, this accomplishment will set the stage for studies in primates and hasten the day when MGE cells may be used as patient therapy for a wide variety of debilitating neurological disorders.

Statement of Benefit to California:	This collaborative proposal promises to accelerate progress toward a novel cell based therapeutic agent with potentially widespread benefit for the treatment of a variety of grave neurological disorders. The promise of this work to eventually help our patients is our primary motivation. Additionally, our studies, if successful, could form the basis of a new stem cell technology to produce unlimited numbers of cellular therapeutic products of uniform quality and effectiveness. The production of neurons from stable nerve cell lines derived from human embryonic stem cells is a much-needed biotechnology and a central challenge in embryonic stem (ES) cell biology. Current methods are inefficient at producing neurons that can effectively migrate and integrate into adult brain, and available cell lines generally lack the ability to differentiate into specific neuronal subtypes. Moreover, while many cells resist neuronal differentiation others often take on a glial cell fate. Identification of key factors driving ES cells into a specific neuronal lineage is the primary focus of the current proposal, and if achieved, will generate valuable intellectual property. As such, it may attract biotechnology interest and promote local business growth and development. Moreover, the inhibitory nerve cell type that is the goal of this proposal would be a potentially valuable therapeutic agent. This achievement could attract additional funding from state or industry to begin primate studies and ultimately convert any success into a safe and effective product for the treatment of patients. To produce and distribute stable medicinal-grade cells of a purity and consistency appropriate for therapeutic use will require partnering with industry. Industry participation would be expected to provide economic benefits in terms of job creation and tax revenues. Hopefully, there may ultimately be health benefits for the citizens of California who are suffering from neurological disease.